



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : KUMAR, Vijay
SERIAL NO : 09/437,449
FILED : November 10, 1999
TITLE : PALATABLE, SUSTAINED RELEASE DRUG GRANULES

Grp./A.U. : 1615
Examiner : Kulkosky, P.
Conf. No. :
Docket No. : P04176US0

#8508
4-11-01

RULE 132 DECLARATION OF DR. VIJAY KUMAR

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Dr. Vijay Kumar, hereby declare the following:

1. I am the inventor of the invention set forth in Serial No. 09/437,449.
2. I have obtained bachelor of science degrees in chemistry, zoology, and botany from Kanpur University in India. I received a master of science in degree in chemistry from Lucknow University in 1972, and a Ph.D. in chemistry from Lucknow University in 1976, and also from Concordia University in Montreal in 1981. My postdoctoral work has been in the areas of pharmaceutics and chemistry. A copy of my Curriculum Vitae is attached.
3. From 1992-1996, I was a clinical assistant professor in the pharmaceutics division of the College of Pharmacy, University of Iowa. From 1996 to present I have been an assistant professor of the pharmaceutics division of the College of Pharmacy, University of Iowa.

4. I have conducted and supervised numerous pharmaceutical research projects since 1993. These projects have dealt primarily with pharmaceutical excipients and formulation techniques.

5. The Examiner's contention that a PVP mixture with PVAP as an additive would be obvious in view of "the known plasticizing properties of PVAP" is not accurate.

6. I am not aware of any previous reports of PVAP used as a plasticizer.

7. In order for PVAP to serve as a plasticizer, it must be miscible with PVP, which it is not.

8. Further, PVAP/PVP complex dries to form a hard material, which indicates that there is no plasticization effect by either the PVAP or PVP.

9. The Examiner's contention that the claimed drug entrapment procedure cannot be generalized for drugs other than ibuprofen is not accurate.

10. Neither of the polymers in the claimed polymer complex forms a complex with the ibuprofen. Instead, the evidence shows that the entrapment of ibuprofen is a physical process. This indicates that persons skilled in the art that all drugs that have the claimed solubility profiles are useful in the invention.

11. To demonstrate that ibuprofen does not interact with PVAP or PVP, each polymer was reacted with ibuprofen, separately, under the identical conditions described under Preparation Method A on p. 20 of the specification.

12. The processing of ibuprofen in the presence of PVP produced a cloudy suspension, which had to be centrifuged in order to obtain the powder for analysis by the powder X-ray diffraction and infrared spectroscopic methods. The infrared spectrum (see attached FIG. 1) of the treated sample was identical to that of the untreated sample. The powder X-ray diffraction pattern (FIG. 2) of the treated sample showed the same peak pattern as that of the raw ibuprofen, but the peaks were weaker in intensity. PVP is highly water-soluble and, hence, remained in solution.

13. The processing of ibuprofen in the presence of PVAP resulted in an immediate precipitation of a fine powder, which was characterized by infrared spectroscopy to be a mixture of PVAP and ibuprofen. This was not surprising because PVAP, owing to the presence of the carboxylic group, is known to precipitate in low pH acid solutions. The infrared spectra of the powdered sample collected and that of the raw ibuprofen are shown in

FIG. 3.

14. The powder X-ray diffractogram of the powdered sample showed the same peak pattern as was observed for the other samples of ibuprofen (i.e., raw and treated ibuprofen), except for that the peaks were much broader and weaker in intensity (FIG. 2).

15. In my opinion, the broadening and reduced intensity of peaks are due to both partial amorphinization of ibuprofen during processing and the presence of PVAP, an amorphous material as an impurity in the sample.

16. Interestingly, the PVAP-ibuprofen coprecipitate readily and completely dissolved in 95% aqueous ethanol. In contrast, the PVAP/PVP complex entrapped granules of ibuprofen, when suspended in the same solvent, allowed the dissolution of ibuprofen only. The PVAP/PVP complex remained insoluble. Further, the coprecipitate exhibited a bitter taste, whereas the granules were palatable.

17. The results of this study indicate that: (a) PVAP alone cannot entrap ibuprofen; and (b) the coprecipitate is a physical mixture of PVAP and PVP, not a complex.

18. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: 4/2/01

Vijay Kumar

Dr. Vijay Kumar

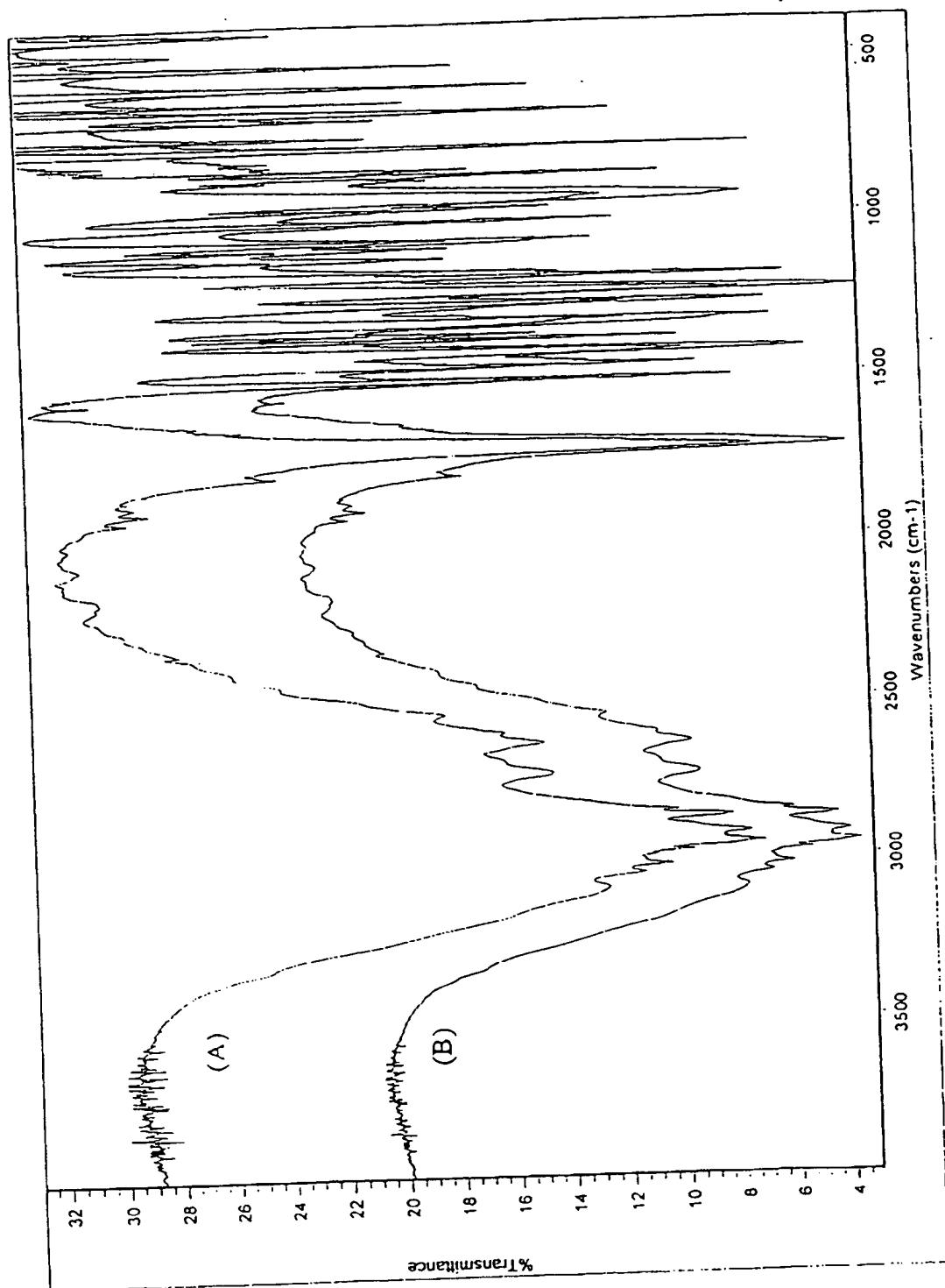


Fig. 1. Infrared spectra of (A) ibuprofen as received and (B) ibuprofen processed in the presence of PVP.

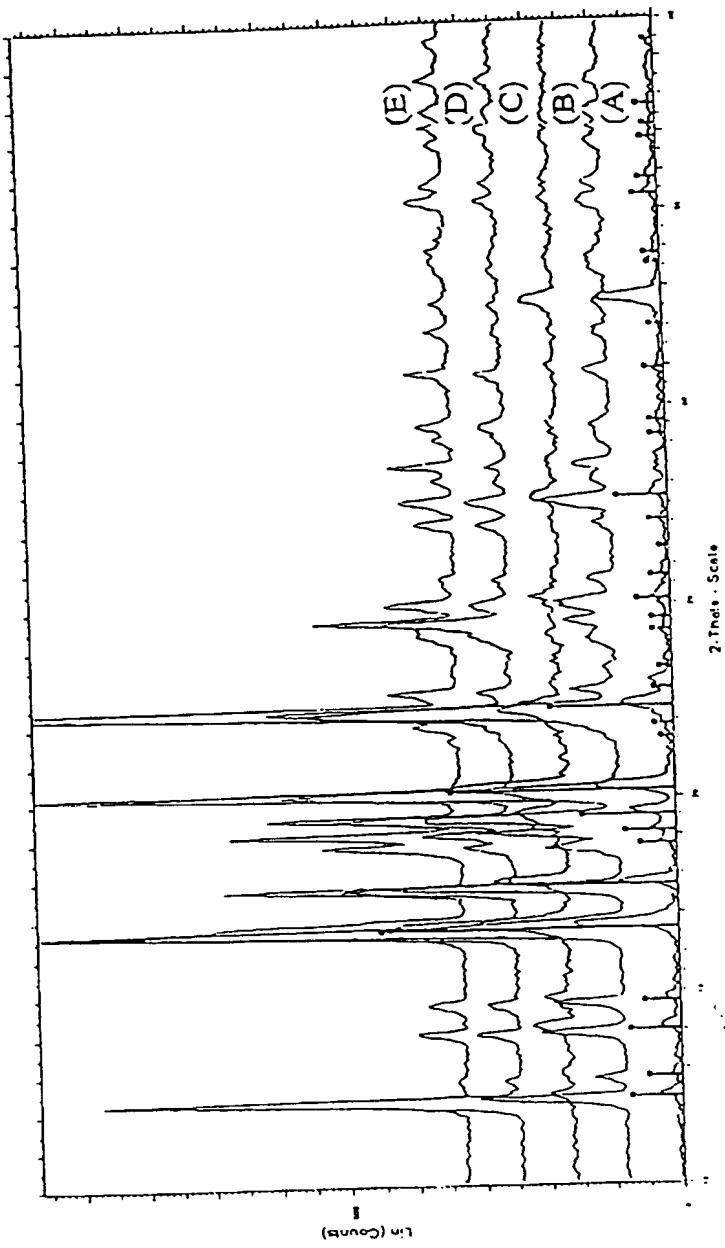


Fig. 2. Powder X-ray diffraction patterns of (A) PVAP-PVP-ibuprofen, (B) ibuprofen as received, (C) ibuprofen processed in the presence of PVP, and (D) ibuprofen processed alone, according to the procedure of this invention. (■ XRD pattern of ibuprofen - Source: Siemens Diffrac Plus; Eva Version 2.2)

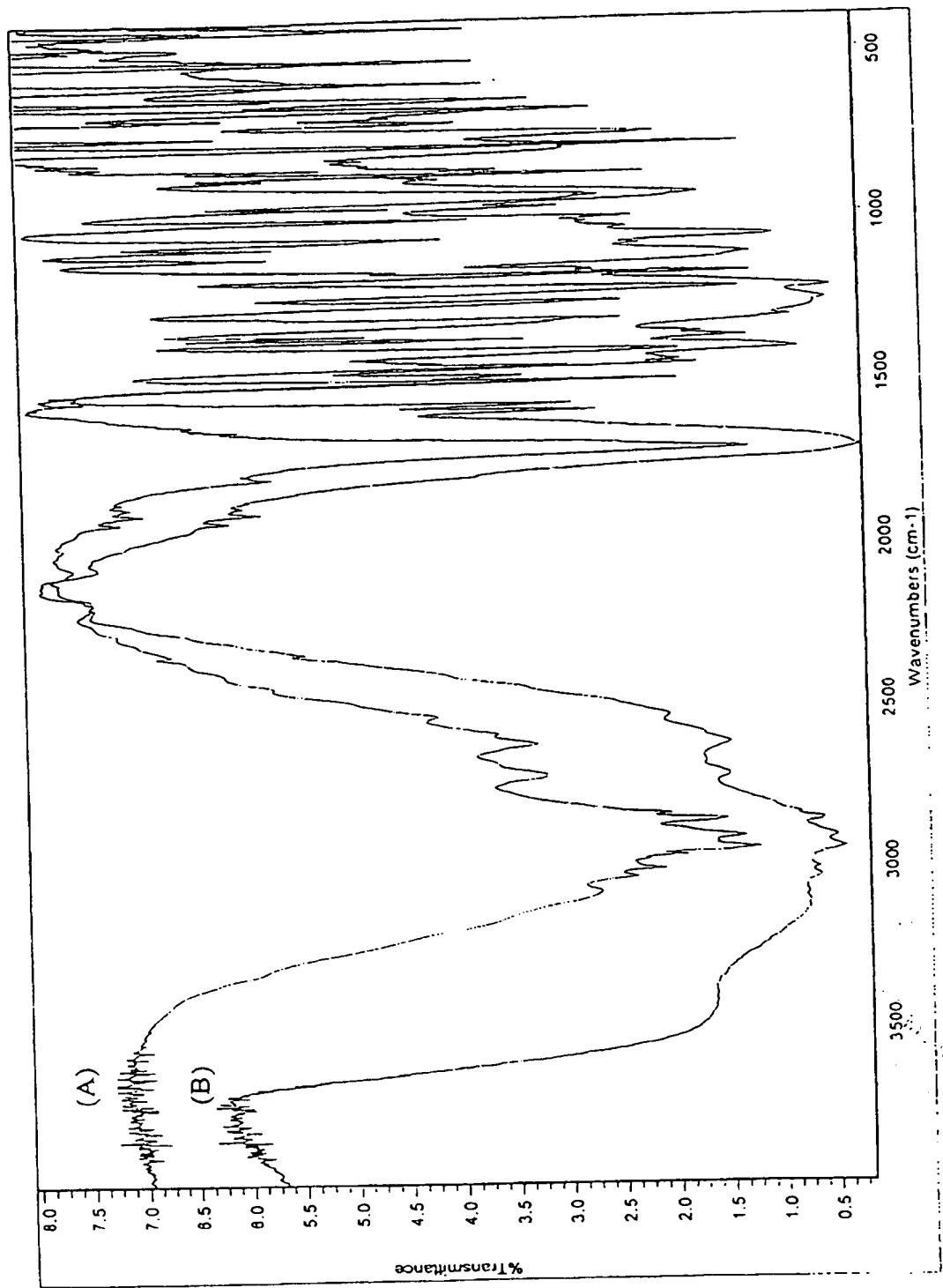


Fig. 3. Infrared spectra of (A) ibuprofen as received and (B) ibuprofen processed in the presence of PVAP.